札幌医誌 5 (4), 205～214 (1954)

The "Modelable Bone" as a New Homograft

By

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Preserved Bones and Recent Advances in Bone Grafting

In modern orthopaedic surgery bone grafting is a common place operation. And in this field the supremacy of fresh autogeneous grafts is generally being taken over by homogeneous grafts. Evidence of the above trend may be seen in the successive establishments of bone banks throughout the world.

From the view-point of results of grafting the fresh autogeneous bone is the best. But this method is not without its defects.

1) In autogeneous bone grafts, the grafts have to be removed from other parts of the patient's bone structure and transplanted immediately. It not only increases the physical burden of weakened, old, or too young patients, but in addition may add and induce long suffering on account of defects after removal of graft bone. Moreover there are cases, in which more bone is required than the patient can supply.

Application of homogeneous bones can eliminate all such difficulties as described above, lessening the sufferings of the patient and speeding operations. However its most important meaning lies in the fact, that it has led, following its natural course, to the preservation of grafts.

Carrel[1] (1912) was the first to transplant preserved chilled bone clinically. But twelve years prior to this the first report on grafting of boiled bones was made by Groose. However the boiled bone, with its usual inferior results, is a dead bone, and therefore can not be considered as a preserved graft.

The recognized methods to date are immersing in chemicals and refrigeration. The former originates in "Os purum" (Orell, 1933[2]), which was prepared by immersing in an alkali or aceton solution. But "Os novum" which is obtained after short-termed subperiosteal transplantation under crista tibiae of the patient was determined too fragile to be utilized in clinical operations (Stark, 1940[3]) Recently several authorities in U.S.A. are using merthiolate solution, which the author has never utilized and, to his regret, can not comment upon.

Kenji Kawamura[4] in Japan and Inclan[5] in Cuba (1942) were the first to report on the preservation of bone grafts at lower temperature. Both of them stored grafts at 0～5°C by immersing in various "preserving solutions," e.g. blood serum, saline solution etc. These cold-storage methods are characterized by the "wet system" as described above. However in the deep refrigeration methods at a far more lower temperature e.g. −10～−35°C a "dry system" is adopted in which the freezing medium is not a liquid but the air itself (Bush 1949[6], Converse & Campbell 1950[7], B. Kawamura 1951[8], Wilson 1951[9],[10], Herbert 1951[11]). This is the method which is being utilized

* Co-operated by T. Hoshii, T. Utsumi, T. Yanagida, Y. Shichinoye, A. Hamada in the Department of Orthopaedic Surgery, Sapporo University of Medicine.

1) Carrel, A.: J.A.M.A. **59**, 523 (1912).
2) Orell, S.: Acta Chir. Scand. **74**, Supplementum 31 (1933).
3) Stark.: Zbl. Chir. **69**, 824 (1940).
4) Kawamura, K.: J. Japanese Surg. Society. **7**, 892 (1942).
5) Inclan, A.: J. Bone & Joint Surg. **24**, 81 (1942).
6) Bush, L.F.: J. Bone & Joint Surg. **29**, 620 (1947).
7) Converse, J.M. & Campbell, R.M.: Plast. Reconstr. Surg. **5**, 258 (1950).
8) Kawamura, B.: J. Jap. Orthop. Surg. Society. **25**, 174 (1951).
9) Wilson, P.D.: J. Bone & Joint Surg. **33-A**, 307 (1951).
10) Wilson, P.D.: J. Bone & Joint Surg. **33-B**, 301, 316 (1951).
11) Herbert, J.J.: J. Bone & Joint Surg. **33-B**, 316 (1951).

in the majority of bone banks.

A comparison between the two has been discussed from the view-point of antigen-antibody reaction. Kenji Kawamura[12], one of advocates of a wet system, asserts that an immersing in a certain preserving solution is indispensable to desensibilize bone grafts, which without this manipulation would render the transplantation useless.

It might be said that the above originates in Orell's opinion[13]. He described that a homogeneous bone grafting could result in a success only in the absence of antibodies in grafting beds, and to achieve this end, the soluble proteins in bone grafts had to be removed by e.g. boiling. However blood-type antigens A and B have been proven to be absent in the cortex of bone by Boyd[14], and the author himself has obtained highly satisfactory clinical results, using homogeneous cortex bone with part of the marrow remaining. Grafts stored in dry system have been transplanted homogeneously in 43 cases with a success of 88%, which apparently surpasses the 75% in wet system reported by Inclan. It would be said, therefore, that Antigen-antibody reaction has scarcely any effect upon a practical grafting, presumably due to lack of said antigen.

In any event, due to the shorter length of preservation of the chilled bones at 0～5°C preferences lies with the deep frozen grafts. Histologically, in a specimen, which had been stored 105 days immersed in a heparin-plasm solution at 5°C, only a half of the bone cells were observed to survive (K. Kawamura[15]). But this was the maximum. In the almost all preserving solutions, the bone cells did not survive over 5 weeks. The metabolism examined in iliac bone of dogs with P^{32} was observed only within 6 weeks (Kiehn 1950[16]). The longest term of preservation of successful clinical cases hitherto reported is 63 days by Inclan[5]. On the other hand, in deep refrigerated specimens, bone cells were seen alive in 51-days-stored human and 91-days-stored rabbits ribs (B. Kawamura & Utsumi 1951[8]). And a report of clinical success was made by Herbert[11] in a bone graft preserved 649 days (1.8 year) at -10°C.

However, the equipment required for such a deep refrigeration is expensive and the processing is difficult, and naturally steps must be taken to overcome these deficiences.

The author has attempted to create a new bone graft material, which can be preserved, holding its availability longer than any other preserved bone, and be handled, stored, carried with ease. In 1951 he has found its realization in the freeze-dried bone chips, termed Modelable Bone. In this thesis his intent is to report studies which have been conducted since the first clinical grafting in the autumn of 1951 and his maiden report at the Annual Assembly of the Japanese Orthopaedic Surgical Society in April of 1952.

Just before the first report of his work, the author read the success of the freeze-dried bone graft by Kreuz and Hyatt in U.S.A. However, since their method is to refrigerate-dehydrate bones in their original shape and size, it differs thoroughly from the author's method which is characterized by crashing bone into chips in order to reduce dehydration time, to simplify the sterilization and then to model or mould them into any shape operation requires.

Production and Properties of the Modelable Bone

Fresh human bone fragments are reduced to chips or particles in an aseptic condition by employing a pulverizer. The chips are then frozen rapidly in a glass receptable immersed in dry-ice-ether (-80°C), and dehydrated in a vacuum. For experimental purposes the apparatus as illustrated in *Fig. 1.* was employed to dehydrate fresh ground bone chips. The apparatus comprises a vacuum pump (1), a tube enclosing P_2O_5 (2), a mercury diffusing pump (3), a Mac Leod gauge (4), a trap or a vacuum bottle surrounded by dry-ice-ether (5) and another thermos bottle containing $CaCl_2$ (6), in which fresh dry bone chips contained in another glass tube (7) is enclosed. The mercury

12) Kawamura, K.: Rinsho Geka (Clin. Surg.) **1** (4), 10 (1947).
13) Orell, S.: J. Bone & Joint Surg. **19**, 873 (1937).
14) Boyd: Fundamentals of Immunology (1947).
15) Kawamura, K.: Rinsho Geka (Clin. Surg.) **1** (2), 11 (1947).
16) Kiehn, C.L.: Ann. Surg. **132**, 427 (1950).

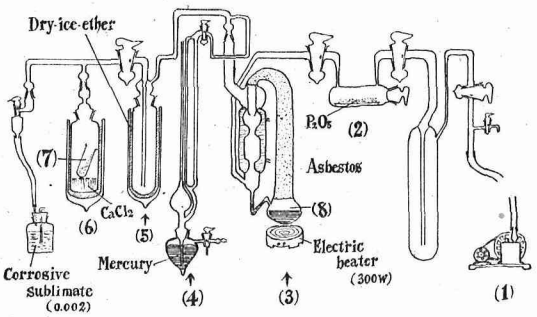


Fig. 1. Equipment for Freeze-dehydration

diffusing pump (3) is provided with a vessel containing mercury (8), which is heated by means of an electric heater. The vacuum pump (1) is operated and, when a vacuum of more than 10^{-2} is reached, the bottle (6) is subjected to said vacuum. At cooling the innert temperature of the bone chips falls extremely rapidly, passing the freezing level in a fraction of a second. For dehydrating 10 grams of frozen bone chips, about 10 hours were required, and the weight was reduced to 6.7 grams.

The freeze-dried bone chips thus obtained are termed by the author as "Modelable Bone". To the eye the chips are irregular-shaped particles of the original solid bone approximately from 10 cubic microns to 10 cubic milimeters mingled with particles of periosteum and marrow (*Fig. 2*). The finished product

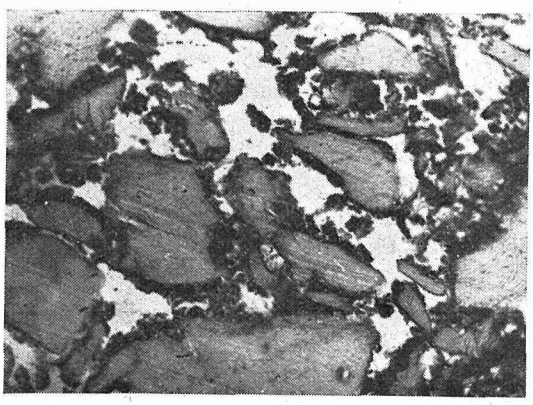


Fig. 2. A microscopic photograph of 3-months-stored Modelable Bone chips. Al-p-tase is dyed black.

can be sealed in a sterile, depressurized glass bottle which can be preserved indefinitely at room temperature or in dark cool storage spaces (*Fig. 3*).

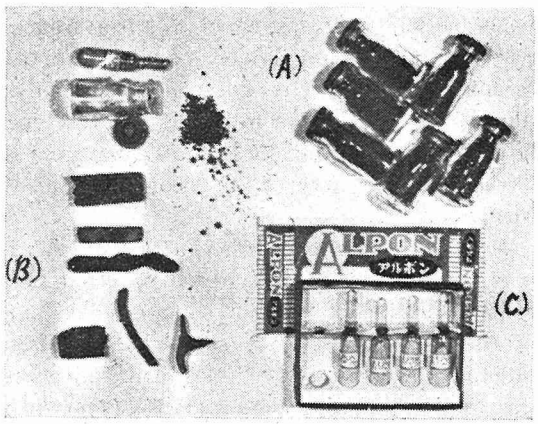


Fig. 3. (A) Bottled Modelable Bone.
(B) Modelable Bone modelled into various types.
(C) "Alpon", a sodium alginate powder.

In processing, one third of the alkali-phosphatase is lost, but the product remains in unchanged condition for months.

Modelling or Moulding of the Modelable Bone, a Preparation Prior to Clinical Application

Modelable Bone can be used as it is. However, by adding or combining other solutions or substances, modelling grafts "made-to-order" are far more useful. The author believes, unless mistaken, that he is the first to succeed in modelling or moulding bone grafts.

How to model Modelable Bone should be determined in accordance with the type of operation. When splinting or retentive power is required, e.g. in a special case of fractures, arthro-or spondylodesis, or Colonna's operation, the grafts must be modelled as a solid body.

However it is a noteworthy fact, that a splinting power of a bone graft, even with the solidity of a tibial cortex, is too weak when unaided. Even when an assisting splint or plaster was applicated, a spontaneous fracture might occur to dislocate the broken grafts from the grafting bed. The author stands against those who overestimate the retentive power of a graft. It can work only temporarily until the reinforcemental bandage is applied.

In fact, the object of clinical bone grafting is in the replacement of defects or the accomplishment of an ossal union of one or more bone and joint surfaces, which, if left untreated, would remain union-delayed or ununited. Splinting by a graft is a secondary factor in almost all cases. The following are the types hitherto utilized clinically in the Department of Orthopaedic Surgery of Sapporo University of Medicine.

1) Type A, termed "*Modelable Bone A*", is a clay-like mixture of kneaded bone chips in a 25% solution of "Alpon" (Commercial name of the Kyosei Co. Ltd. product), a sodium alginate powder (*Fig. 4*). For grafting purposes, the solution should be held at 7.4 PH, which is equal to human tissue fluid. In an operation,

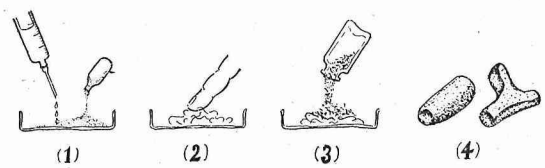


Fig. 4. Modelling Technique of „Modelable Bone A" (1) A 25% sodium alginate solution is prepared by adding aqua destillata of pH. 8.0. (2) The starchy 25% sodium alginate solution is kneaded by the operator with his fingers. (3) Modelable Bone chips are mixed and kneaded well. (4) A Modelable Bone A has been completed. This clay-like, pliable dough can be modelled into virtually any type of graft repuired in operations.

the dough or putty can be applied to virtually any type of bone surface or defect regardless of its irregularity by virtue of its pliability, viscosity and cohesion. In addition, operations are simplified by the coagulating power of sodium alginate.

Since a clinical bone grafting objects to a replacement of defects or the accomplishment of an ossal union as described above, the application of Modelable Bone A can be utilized fully and to the majority of grafting operations.

This method can also be successfully utilized in the grafting of fresh autogeneous or preserved homogeneous bone chips.

2) Type B: "*Modelelable Bone CA*"

"Modelable Bone A", as described above, has the disadvantage of being destroyed as sodium alginate is soluted and is dissolved by bleeding or exudation at the site of the grafting. In such a case an unsoluble graft is required. Modelable Bone CA is the answer to this demand. It is a combination of "A" solidified by adding a 10% $CaCl_2$ solution. This type is elastic, and, though there is a slight question as to its strength, it serves as a temporary splint in operations of small bones and joints in the hand or foot, until the assisting bandage is applied.

3) Type C: "*Modelable Bone G*"

Though the majority of bone graftings can be conducted employing soft grafts, such operations as bone nailing in the un-united femur neck or the aseptically necrosed epiphysis would require a solid graft. Modelable Bone C is a compressed product of Modelable Bone chips plus a 40% gelatine solution (its melting point is between 38～43°C) It has considerable strength in a dry state. But, since it is soon destroyed by bleeding or exudation soon after being transplanted, the operation should be performed skilfully and promptly.

Irritativity of Modelable Bone A

The irritation of the graft on the organism often leads the grafting to a failure. In order to investigate the irritativity of the Modelable Bone A, the author has conducted intramuscular graftings in rabbits' back.

The Modelable Bone chips transplanted in the muscle were gradually absorbed and organized by the newly proliferated granulation. And the solidium alginate solution was dissolved by exudation and then phagocytized by the histiocytes or giant cells. The secondary reaction as a sign of antigen-antibody reaction was not observed. It has been histologically established that the new graft has almost no harm on living tissues.

The irritativity of the sodium alginate solution in "A"-Bone was investigated histologically and radiologically by on-lay graftings in artificially induced grooves in tibiae of rabbits. The healing process of the bone wound was favorable, and absolutely no evidence of delayed healing was found.

It is well-known, that the antigen-antibody reaction is a strong fortress against the suc-

cessful homogeneous graftings. And as to the bone grafting, the desensibilization of the graft has been asserted as an essential preparation by some authorities (Orell, K. Kawamura). But, practically speaking, it leaves considerable doubt.

The absence of aggultinogens A and B in the cortex of bone was previously described by Boyd[14] (1947). In bone marrow, its presence was established by the author and his cooperator Utsumi[17]. And though Modelable Bone contains both corticalis and marrow, serum agglutination was not observed. Besides, in 23 patients who were subjected to Modelable Bone graftings, precipitative reaction in serum was investigated weekly for 5 weeks and in no cases were the results positive. The reason probably lies in the fact that the modelable bone is "polyvalent", since it is prepared by mixing bone chips of various blood types.

Experimental Graftings

The author has conducted experimental studies on grafting Modelable Bone A with radiological and histological findings as follows.

A) Transplantation as an on-lay graft

The author transplanted "Modelable Bone A" in a groove chiselled in the tibial crest of rabbits and observed the healing process roentgenologically and histologically for a period of 14 weeks. The A-Bone after the transplantation increases in bulk by absorption of tissue fluid and commences to deteriorate with the melting of the modelling material, which is replaced by newly proliferated granulation. By this granulation the bone chips were held in their original positions (*Fixation in the connective tissue*). The entire process is in line with general bone chip grafting operations. It is also noted that solium alginate stimmulates proliferation of the connective tissue.

The proliferation of the newly formed bone tissue reaches its meridian in 3~4 weeks. At the end of the 5th week the bone wound is healed almost completely, showing reconstructive process at the 6th week. The results are not as satisfactory as in case of autogeneous grafting, but surpasses the results of refrigerated grafts. However it can be safely said, that Modelable Bone as grafts have been proven useful.

The process of grafting "Madelable Bone A" differs from that of the autogeneous grafts as follows:

(a) The uniting tissue of the autogeneous grafts with the host varies from granulation to osteoid and then to bone tissue in order. But the modelable bone chips or particles, after wrapped or fixed by granulation are connected to each other by branches of trabeculae derived from the host and turn gradually into bone tissue.

(b) Reactive endosteal bone proliferation in modelable bone cases is far more properous than that of autogeneous grafts.

(c) Cartilagineous tissue in autogeneous cases is found more frequently than in modelable bone cases. Since the grafts used in the former are considerably larger in size than the latter, the cause may be due to a slight shifting of the former.

B) Transplantation in a large defect as an bridging graft.

Results were favorable. 3~16 mm defects

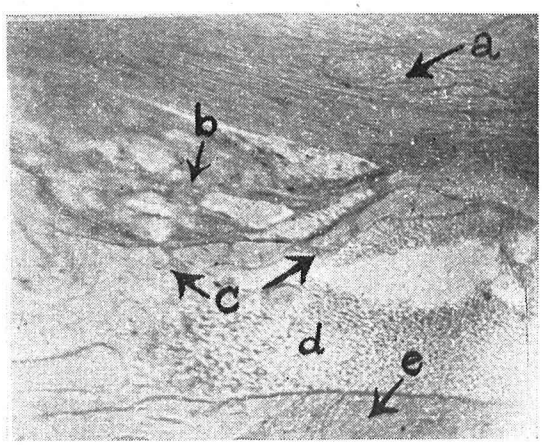


Fig. 5. A microscopic photograph of rabbit radius defect of 9 weeks after being bridged using "Modelable Bone CA". The defect has already been replaced almost completely by new bone which has proliferated in grafting region.
a : Granulation tissue.
b : Osteoid tissue containing Mod. Bone chips.
c : Bridge of new-bone islands.
d : Newly-formed bone marrow.
e : Corticalis of the opposite side (without grafting)

17) Kawamura, B. & Utsumi, T.: Sapporo Med. J. 5, 54 (1954).

were made in rabbit radius, and to bridge these defects "CA" and "G" were transplanted, resulting in an early ossal union. For instance, in one of the experimental rabbits grafted with "CA", a 3 cm defect showed radiologically an ossal union with proliferation of new-bone in the ulnar region before the end of the 4th week. As for the histological findings at the end of the 9th week new cortical bone had been formed on the ulnar side, while on the radial side a chain of cortical bone islands was observed. The intervening space was already filled with newly formed marrow (*Fig. 5*).

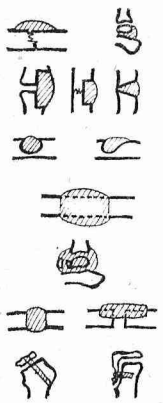
Clinical Results

Since Autumn 1951 to April 6th 1954 Modelable Bone grafts were utilized for various purposes at the Orthopaedic Surgical Department of the Sapporo University of Medicine. Analysis of the various operative procedures is presented in *Table 1.* It will be seen, that they contain almost all disorders, which have been hitherto considered as indications

Table 1. *Technique and Conditions in which Modelable Bone Grafts have been used*

Arthrodesis	*28*
Tuberculous arthritis	10
Paralytic foot deformities	15
Others	3
Arthrorisis	*5*
Paralytic drop-foot	5
Spine fusion	*1*
Spondylolisthesis	1
Osteosynthesis	*24*
Un-united fractures	6
Delayed union	8
Others	10
Replacement of defect	*14*
after removal of benign tumor	11
after removal of osteitis fibrosa loc.	1
after saucerization of osteomyelitis	1
Others	1
Osteotomy defect replacement	*21*
Ankylosis of joint	3
Bowleg resulting from ricket	4
Others	14
Bone nailing	*18*
Aseptic necrosis	17
Others	1
Shelf-operation	*5*
Congenitally dislocated hip	5

of bone grafts. Each technique represented in *Fig. 6* was chosen in accordance with operation requirements and observed for 8～32 weeks clinically and radiologically. Out of a total of 101 patients or 116 cases, 99 patients or



1) Onlay graft.
2) Inserting or inlay graft.
3) Plugging.
4) Surrounding.
5) Wrapping.
6) Bridging.
7) Nailing.

Fig. 6. Transplantation Methods of Modelable Bone.

104 cases (77.7%) of the total were checked for final results. 43 were *excellent*, 43 *good*, 11 *fair*, 4 *poor*, and *failures* were seen only in 3 cases. Three cases of the failures were caused by suppuration while the other became ununited. In short, 97 cases or 93.3% of the 104 were as success and it can be said that these results are all highly satisfactory.

In several operations the autogenous bone

Table 2. *Age of Grafts and Results of Its Grafting*

Results	Age (week)																		To-tal
	1	2	3	4	5	6	7	8	9	10	11	12	16	18	20	53			
Excellent	2	11	10	1		1	7	4	2		1		2	1		1			43
Good	7	5	7		1	3	5	2	5	2	1	3		1		1			43
Fair	3	1	2		1			2						1	1				11
Poor	3	1																	4
Failure		1				1		1											3

chips removed at the site of the operation were utilized additionally.

The Modelable Bone utilized in the above mentioned operations had been preserved from 1 to 53 weeks (371 days) (*Table 2*), and the difference of the length of preserving had absolutely no effects on the operations.

The author compard, as shown in *Fig. 7*, temperature and pulse charts of two groups of 8 patients respectively. The first group consists of cases in which osteosynthesis was performed in a single operation, using fresh autogeneous grafts. The second group is of cases in which Modelable Bone grafts were used for the same purpose. It was revealled that the physical burden on patients in which Modelable Bone was used were considerable lighter.

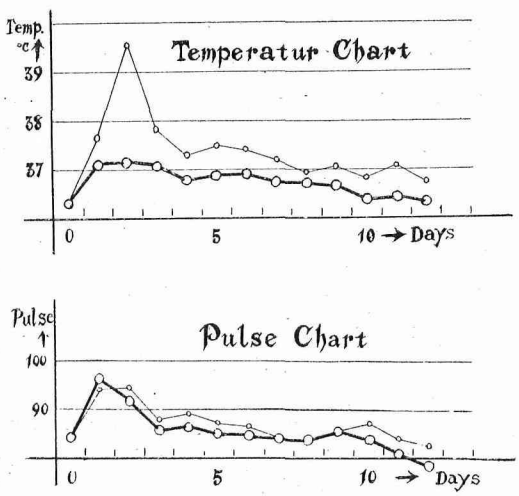


Fig. 7. A comperative chart of postoperative temperature and pulse. Thin lines indicate the average of the cases in which osteosynthesis was performed in a single operation, using fresh autogeneous grafts. Heavy lines indicate the same as above of cases, in which similar operations were performed, utilizing Modelable Bone grafts.

Precautions in Transplantation

In Modelable Bone Grafting the following points must be adhered to:

1) Modelable Bone chips should be used generously to ensure success. When the grafts are not sufficiently large enough, results are not favourable. This may be said for fresh autogeneous grafts and for modelable bone also.

2) Blood must be stanched completely, since excessive post-operative bleeding dissolves the modelled product and scatters the Modelable Bone chips out of the site of grafting, preparing a favorable condition for proliferation of germs.

3) After grafting of *Modelable Bone A or G*, soft tissues such as periosteum and muscles should be ligated closely. Without this manipulation, the scattering of Modelable Bone chips can not be avoided.

4) It should always be remembered, that the irritative activity of *Modelable Bone CA* is rather severe. It is absolutely necessary, that the graft be washed throughly in a saline solution, before being transplanted.

5) *Modelable Bone G* does not attain sufficient rigidity, when dried only for an insufficient time. Modelling should be completed one day prior to the operation.

6) *Modelable Bone G* has a tendency of softening quickly. Hence, in transplantations such as nailing, the operation should be performed as quickly and skillfully as possible.

Discussion

Wherein lies the superiority of Modelable Bone grafting? The answer surely is in the fact that this graft is produced by means of freeze-drying, which has been improved by many authorities since Altmann (1890[18]) and Shackell (1909[19]) and recently utilized widely in long-term-preservation of various biological materials, drugs and foods.

The survival of cells of bone graft has been hotly debated. Tomita and Axhausen described that the endosteum and the tissues in Haversian canal survived, but this was met with opposition previoulsy by Baschkirzew-Petrew[20] and recently by Reynolds[21]. New-bone formation in a drilled hole or a saw cut in an intramusclar bone graft of dog was reported by Wilson[22], but Utsumi[23] in our institute could not observe the same phenomena in the same grafts of rabbit. If on the other hand the cells in the bone graft could survive and could form bone itself, the bone productive power would be limited.

The author opposes those who overestimate the bone producing power of bone graft. He

18) Altmann, R.: Die Elementarorganismen u. ihre Beziehungen zu den Zellen (Leipzig, 1890).
19) Shackell, L.F.: Am. J. physiol. **24**, 325 (1909).
20) Baschkirzew u. Petrow: Z. Chir. **113**, 490 (1912).
21) Reynolds, F.C. & Oliver, D.R.: J. Bone & Joint Surg. **32-A**, 283 (1950).
22) Wilson, P.D.: J. Bone & Joint Surg. **33-B**, 301 (1951).
23) Utsumi, T.: Sapporo Med. J. **5**, 135 (1954).

believes that *the practical significance of the free bone graft lies not always in the active new-bone formation, but in supplying "materials" necessary to a bone union.* And the reason why we want as many cellular components to live in graft lies in the hypothesis, that the more fresh the materials contained in graft *biologically and chemically*, the more excellent the results of graftings are as a result of the stimulating effects on the grafting bed and the surrounding tissues.

However, the word "materials" necessary to a bone-union are not only a $Ca_3(PO_4)_2$, a $CaCO_3$, a CaFl, or a $MgHPO_4$ etc. And many attempts have been made by others in order to complete ossal union by the local injection of these anorganic chemicals but satisfactory results have not been obtained. *Why is the fresh autogeneous graft superior? It is simply because it is bone tissue as a whole and has therefore all the components of bone either known or unknown.* In other words, besides the components which are used as "materials" in a narrow sense, which contributes directly to the bone formation, there are possibly certain unknown factors, which contribute indirectly by stimmulating the grafting beds and the surrounding soft tissues.

Since the Modelable Bone grafts are prepared by the freeze-drying, it is only natural that the Modelable Bone grafts give satisfactory results.

From the enzyme view-point, the bone grafts should be preserved below −10°C, at which their autolysis is strictly avoided by inactivilizing the proteolytic ferment, this is the reason why the available preserving term of deep-refrigerated bones is longer than of bones chilled at 0～5°C. However, the Modelable Bone is not effected by the action of the enzyme. This supports theoretically the maintenance of freshness of Modelable Bone, which has been preserved for years.

Conclusions

"Modelable Bone" (freeze-dried bone chips) is an excellent new homograft, which has the following merits:

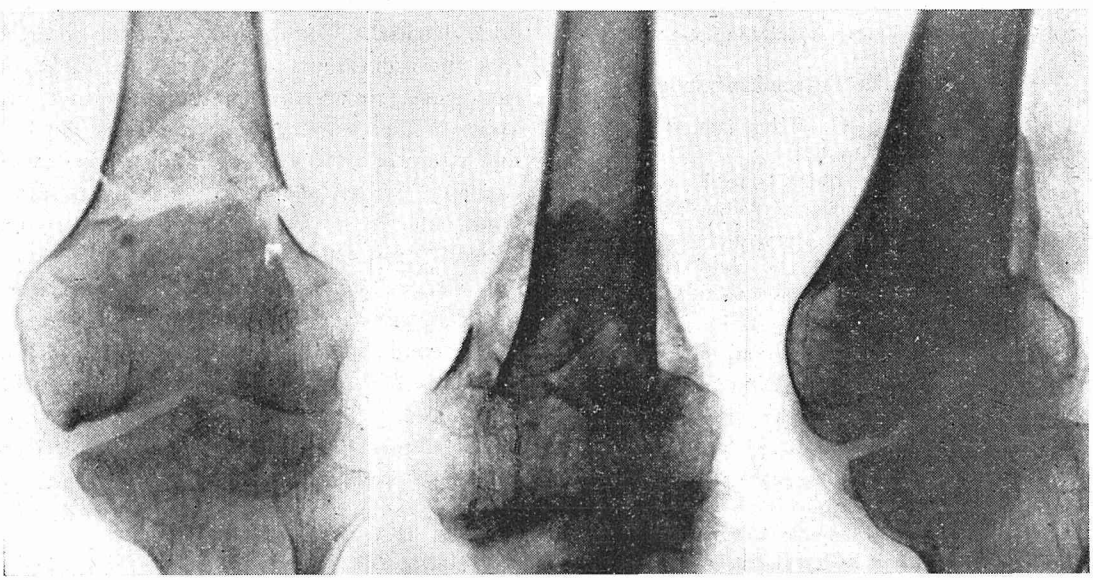
a) It can be modelled to fit any operation requirements. It not only reduces operation time, but makes grafting a much simpler and easier matter.

b) It can be preserved at room temperature for a fairly long period of time. No special storage is required, thus making bone banks obsolete.

c) It can be sealed in a small sterilized bottle, which makes handling a simple matter and eliminates transplantation difficulties. The bottles may be sent by mail or hand-carried.

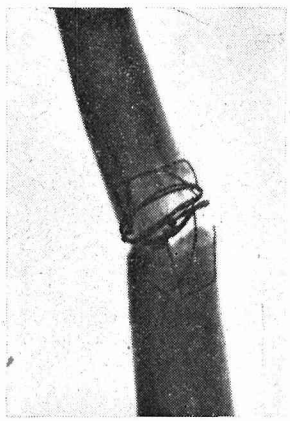
d) It can be accumulated in sufficient quantities to cover any amount required in operations. Replenishing of supplies should be fairly easy. It can be mass-produced.

(Received April 10, 1954)

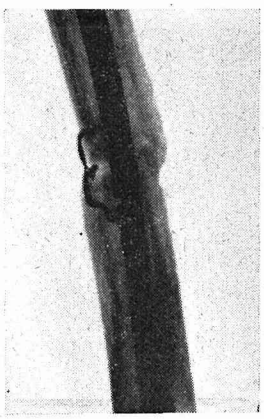


(a) Preoperative photograph. (b) 4 weeks after treated with "Modelable Bone A" grafting (c) 25 weeks after operation.

Fig. 8. Delayed union of femur fracture.



(A) Preoperative photograph.



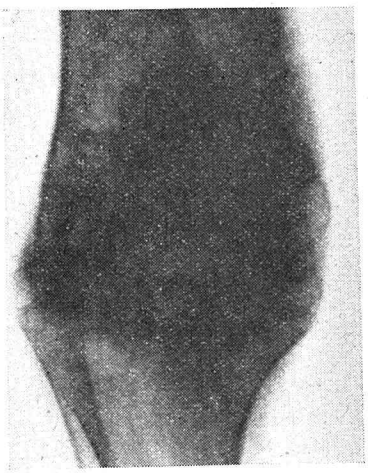
(B) 13 weeks after inserting Mod. Bone A.

Fig. 9. Non-union of humerus.

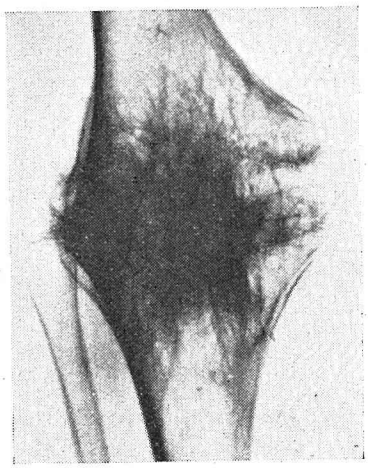
(A) Preoperative view. (→: Focus)

(B) 7 months after implantation of Modelable Bone. The focus has been obliterated completely by new bone formation.

Fig. 10. Tuberculosis of sacro-iliac joint.



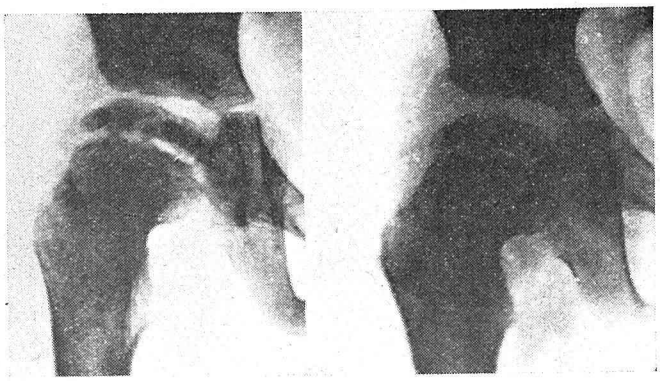
(A) Preoperative photograph.



(B) 5 months after intraarticular arthrodesis with Modelable Bone A. Ossal union was already completed.

Fig. 11. Tuberculosis of knee joint.

(A) (B)



(A) Preoperative view. The head shows flattening and many islands of hypercalcification.

(B) The head remains flattened, but the bony islands have coalesced and the density of the epiphysis has become uniform.

Fig. 12. Legg-Perthes' disease.